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of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

Contents

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HISTOPLASMOSIS*

A Report of Four Cases, Two in Siblings, from the Children's Hospital, Washington, D. C.

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Introduction

Histoplasmosis was first observed and described by Darling[1] in Panama in 1906. His 3 cases were in adults[1–3] and the first 3 cases reported from the continental United States were in persons above the age of 40. The observation of additional cases showed that the disease was not confined to the tropics nor did it occur only in adult life. In 1934 Dodd and Tompkins[4] reported a case of this mycosis in a 6 months old child living in Tennessee. The diagnosis was made during life and the fungus was first isolated in culture and identified by De Monbreun[5]. In the excellent summary review of the disease made by Parsons and Zarafonetis[6], they point out that in 11 of 60 cases for which age data were available the patients were less than one year of age. Thereafter the frequency of histoplasmosis appears to drop sharply, rising again to a plateau in the age group ranging between 40 and 70 years. Histoplasmosis is of special interest to pediatricians not only because of its apparent predilection for infancy, but also because of the suggestion made by a number of investigators that this mycosis, fatal in nearly all recognized cases, may occur in a benign form which is now unrecognized and that therefore it may be much more common in childhood than is generally supposed. The apparent increase in the number of recognized cases may possibly be due to its more frequent recognition now than formerly rather than an absolute increase in its frequency. However, some investigators believe that the actual incidence of the disease is definitely on the increase.

The following report represents a clinical summary of 4 cases of histoplasmosis which have been seen in Children's Hospital, Washington, D. C. Two of the cases, hitherto unreported, occurred in brothers and represent the first reported instance of histoplasmosis in siblings. The other two cases have been previously reported[6, 7] and will be reviewed briefly. These four cases are presented because they raise important epidemiological considerations. All four patients were children living in Loudon County, Virginia, within a radius of 8 miles from Leesburg suggesting that there may

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be in this rural area an unusual geographical concentration of the mycosis. In addition, the occurrence of histoplasmosis in siblings suggests that there may have been transmission from one person to another. These circumstances will be considered in more detail after presentation of the case reports.

Case 1

S. D., a 7-year old white male, was first admitted to the Children's Hospital, Washington, D. C., on December 13, 1944, with the chief complaint of "swelling in the neck."

Approximately 8 weeks before admission, the child's mother noted bilateral enlargement of the glands in his neck. His local physician was consulted after the glands had been present for one week; and sulfadiazine was prescribed without improvement. During this time there was no fever. The cervical glands, especially on the right, became progressively larger until his first admission on December 13, 1944.

The patient was born and raised in the town of Ashburn, Loudon County, Virginia, and lived there since birth, not having traveled beyond a radius of some 20 miles from Ashburn during his entire life. A younger brother, aged 6 years, was the only living sibling and at that time was in good health. The family drank pasteurized milk and well water. They kept chickens and two hogs but had not permitted the boys to have a dog or other domestic pets.

Physical examination revealed a well developed, well nourished white male who was not acutely ill. Lymph glands in the cervical and sub-maxillary regions were enlarged particularly on the right side, the largest being about the size of a small hen's egg. The glands were discrete, freely movable, firm and only slightly tender. The axillary and inguinal lymph nodes were slightly enlarged and discrete. The liver and spleen were not enlarged. A blood count revealed a mild degree of hypochromic anemia with a normal white cell count and differential. All other laboratory tests made at this time were negative.

During his stay in the hospital the patient showed a low-grade fever ranging between 99°–100°. His weight was 55 lbs. A biopsy of a gland from the right side of the neck was taken on December 13, 1944, and reported by Dr. J. W. Lindsay as follows: "Sections show a striking picture with numerous nodules of epithelioid cells, many of which are incorporated into large multinucleated giant cells of the Langhan's-Schuffel type. In some areas there are broad pits of connective and reticulum tissue and in others dense masses of plasma cells. There is a border of somewhat hyperplastic lymphoid tissue and occasional eosinophil cells are noted. The condition is considered to be tuberculosis (or possibly Boeck's sarcoid)

rather than neoplastic. The possibility of some fungus infection might be considered."

X-ray of the hands and feet revealed no evidence of sarcoid deposits or any other abnormality and roentgenological examination of the chest revealed only an increase in bronchovascular markings throughout the parenchyma but no other evidence of abnormality. A tuberculin skin test of $\frac{1}{10}$ mg. old tuberculin was negative. Five days after admission the patient was discharged to be followed at home.

A diagnostic course of x-ray therapy to the cervical glands was instituted, and was given anteriorly and posteriorly to the right side of the neck for 4 weeks. At the end of this time there was a remarkable reduction in the size of the glands, although they never did actually disappear. Further roentgen therapy totaling 3000r was administered during the next 5 months to the various sites of glandular enlargement. The liver and spleen during this follow-up period were never palpable. In view of the clinical picture, the radio-sensitivity of the cervical glands and failure to demonstrate any evidence of tuberculosis, the diagnosis of tuberculosis or Boeck's sarcoid as suggested by the biopsy of the gland was discarded and the probable diagnosis of Hodgkin's disease was favored.

During July, 1945, the patient developed severe abdominal pain and bloody diarrhea. Edema of his lower extremities appeared in September. On October 7, 1945, he was readmitted to the hospital with a temperature of 100.6°, moderate edema of the lower extremities, marked emaciation, and thrush-like lesions in the mouth.

Roentgenological examination of the chest showed a small amount of infiltration in the right base associated with some small areas of calcification at the roots of the lungs. Examination of the blood revealed an increase of the hypochromic anemia and a leucopenia with a normal differential. Repeated blood and stool cultures were negative. Agglutination tests were all negative except for *Salmonella schottmulleri* which was positive in dilutions of 1:20 through 1:2560. Three days later these tests were repeated and again found to be positive in the same dilutions. Several examinations of the blood and stools, however, failed to demonstrate the presence of *Salmonella schottmulleri*. The total serum protein was 3.04 gms. % with an A/G ratio of 1.2:1.

During the entire month of observation in the hospital on this second admission, the patient continued to run a septic fever with the temperature fluctuating between 99° and 104° daily. A proctoscopic examination revealed no ulcerations of the rectal mucosa. Bone marrow smear and culture made on October 19th showed no evidence of histoplasmosis; a histoplasmin cutaneous test in dilutions of 1:1000, 1:100, 1:10, and undilated were all negative in 24, 48, and 72 hours. All efforts to establish a

diagnosis of histoplasmosis in this case were unsuccessful, in spite of the fact that this diagnosis had already been confirmed in the case of his brother who had been admitted to the hospital on September 28 (see case 2).

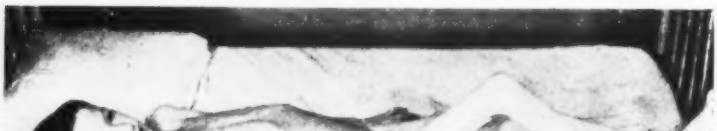

FIG. 1. S. D. (CASE 1) AT THE TIME OF READMISSION TO THE HOSPITAL IN OCTOBER, 1945, ILLUSTRATING THE MARKED EMACIATION

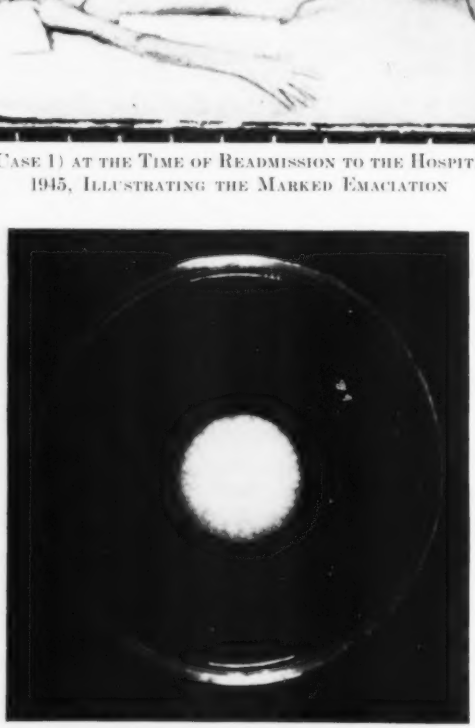

FIG. 2. ILLUSTRATING THE GROWTH OF HISTOPLASMA CAPSULATUM ON SABOURAUD'S AGAR MEDIA

The patient was treated with both sulfadiazine and penicillin without effect. Repeated blood transfusions were given.

Shortly after his brother died of histoplasmosis, the patient was discharged upon the request of his parents. At home, the child continued his

rapid downhill course. At this time, examination and culture of the oral lesions and of stools revealed a large number of thrush fungi. The severe bloody diarrhea continued at home and starting on the 16th of November he began to bleed from the rectum and died three days later on the 19th of November.

Concurrent with the patient's death, *Histoplasma capsulatum* grew in the bone marrow culture, which had been planted on Sabouraud's medium on October 19.

At post mortem examination, the liver appeared to be normal in size. The spleen was slightly enlarged. Most of the gross pathological changes observed appeared in the gastrointestinal tract. Throughout the ileum were found areas of lymphoid hyperplasia alternating with patches of ulceration. Other areas showed marked thickening up to 3 to 5 mm. producing an annular constriction of the wall. On the serosal surface the sites of ulceration imparted a bluish color to the wall and it was evident that there was little more than serosa remaining of the entire wall in these areas. In the terminal ileum, the lymphoid elements were hyperplastic producing a cauliflower-like appearance. In the colon, areas of ulceration and thickening of the wall were also noted. The mesenteric lymph nodes were found to be markedly enlarged.

On microscopic examination, numerous Histoplasma capsulatum organisms were found in the liver, spleen, kidneys, lungs, retroperitoneal lymph nodes, and bone marrow.

Case 2

J. D., a 6-year old white male and the brother of the patient in case 1, was admitted on September 28, 1945, with the chief complaint of fever ranging between 100° and 104° since September 7. There were no other complaints except anorexia and constipation. Prior to the onset of these symptoms, he had been in apparent good health.

The family history and environment were the same as in case 1. He slept in the same bed with his brother during most of the latter's prolonged chronic illness. His past history was essentially negative.

Physical examination revealed a pale, well nourished, 6-year old white male who did not appear acutely ill. The liver and spleen were enlarged about 7 cm. below the costal margin, both organs being smooth, non-tender and firm with sharply defined borders. The anterior and posterior cervical lymph glands were slightly enlarged, discrete, and non-tender. His temperature upon admission was 100°, and during his entire stay in the hospital fluctuated between 100° and 104°.

A hemogram revealed a marked hypochromic anemia with a normal white blood count and differential. All other laboratory tests made at this time were negative.

X-ray examination of the chest revealed a moderate infiltration throughout both lungs, more marked in the upper half of the right lung and interpreted as representing bronchopneumonia. Intra-dermal tests for

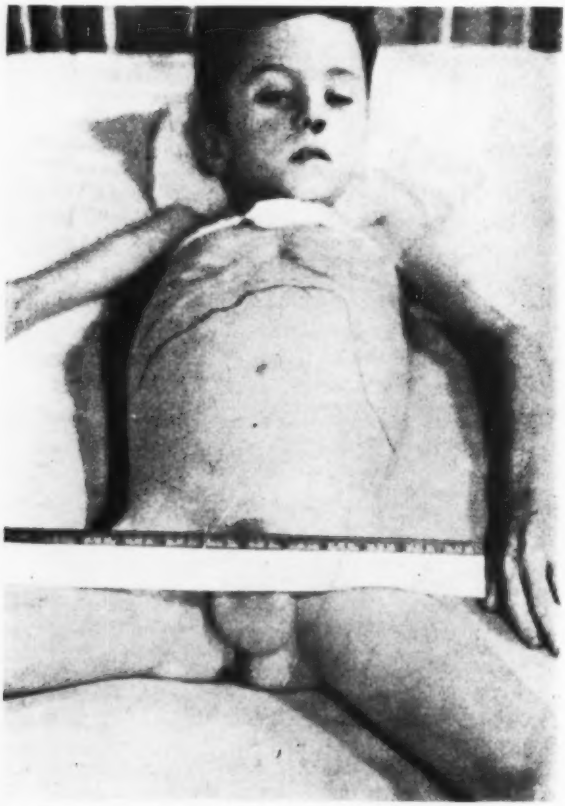

FIG. 3. J. D. (CASE 2) AS HE APPEARED ABOUT THREE WEEKS AFTER HOSPITAL ADMISSION IN OCTOBER, 1945

At this time a diagnosis of histoplasmosis had been definitely established by sternal marrow examination. Note the delineation of the hepatosplenomegaly and the area of ulceration about the left nares and perineal region. The degree of emaciation is less marked than that of his brother (Case 1) (see fig. 1).

brucellosis and tuberculosis were negative. The histoplasmin skin test in dilutions of 1:1000, 1:100, 1:10, and undiluted were all negative.

The patient pursued a rapidly downhill course. The spleen and liver

enlarged rapidly. He had several episodes of epistaxis and developed ulcers in the region of the left nares and anus.

Sternal marrow biopsy on October 19 definitely established the presence of numerous organisms having the morphological appearance of *Histoplasma capsulatum*.

Therapy was as in case 1. The patient expired on October 27, 1945, one month after admission to the hospital.

On post mortem examination, the liver and spleen were found to be considerably enlarged. Both organs showed numerous small grayish-white miliary lesions scattered on the surface and throughout. Both lungs

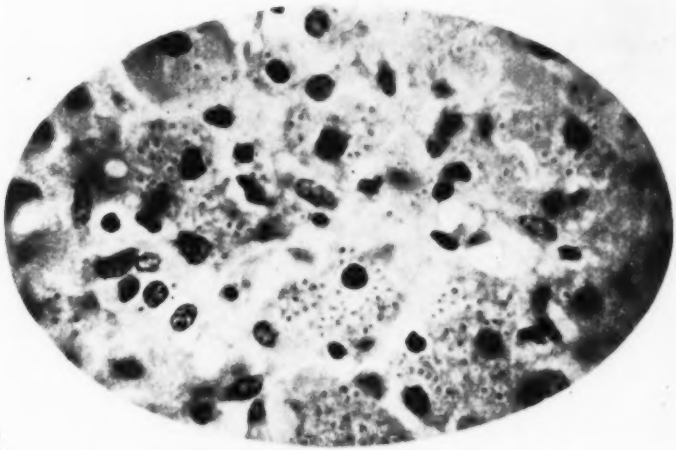

FIG. 4. ADRENAL GLAND IN CASE 3 SHOWING NUMEROUS HISTOPLASMA CAPSULATUM ORGANISMS

showed numerous small areas of consolidation. On microscopic examination these areas were apparently due to pneumonitis. Endothelial cells filled with Histoplasma organisms appeared to predominate. The mesenteric lymph nodes were markedly enlarged. The ileum and cecum showed an occasional ulcer. On microscopic examination, numerous Histoplasma organisms were found in the lungs, spleen, liver, kidneys and bone marrow.

CASE 3 (PREVIOUSLY REPORTED BY SHAFFER ET AL.)[7]

F. C., an 11 month old white female, was admitted to Children's Hospital on July 22, 1938, with a chief complaint of intermittent fever of 6 months' duration. One month prior to entry, the infant exhibited a marked drowsiness accompanied by periods of alternating diarrhea and constipation.

The patient lived on a farm near Paenonean Springs in Loudon County, Virginia, approximately 15 miles from the home of cases 1 and 2.

Physical examination revealed bilateral cervical adenopathy and marked hepatosplenomegaly. Temperature was 103°. Laboratory examination showed a severe hypochromic anemia, and leukopenia with a shift to the left of the white cell series. Tuberculin, Schick, Wassermann, and Kahn tests were all negative.

In view of the presence of hepatosplenomegaly and the blood picture, a clinical diagnosis of aleukemic leukemia was entertained.

The patient's course in the hospital showed a rapid fatal termination. The temperature fluctuated between 100° and 105° during the entire hospital stay. Shortly before death, a small gangrenous, pea-sized area of ulceration was noted on the right ala nasi and became progressively larger. The patient died on August 12, approximately 7 months after the onset of illness.

On postmortem examination, organisms having the morphology of *Histoplasma capsulatum* were found in almost all tissues including the liver, lungs, spleen, mesenteric lymph nodes, kidneys, adrenals, bone marrow, and subcutaneous tissue.

Case 4

C. S., a 4-year old white female, was admitted to Children's Hospital under the care of Dr. Edgar P. Copeland in October, 1922, with the chief complaint of intermittent fever and progressive loss of weight. In March, 1921, 18 months prior to entry, she began to run an intermittent fever accompanied by marked lethargy and loss of appetite. This episode continued for about 3 weeks following which she showed marked improvement and according to the parents, regained her normal health. During the next 8 months, the child appeared moderately well except for periods of high fever and prostration which continued for one or two days and then subsided. In the intervals between these sporadic exacerbations of fever, she appeared moderately alert and active.

Six months prior to entry, she began to lose weight steadily and appeared quite listless. At this time she was admitted to another hospital and was discharged 2 weeks later ostensibly improved. No diagnosis was made at this time.

During the next 6 months, her fever continued in intermittent fashion. She became progressively more emaciated and during this time her abdomen was noted to have become enlarged. About 4 months prior to entry, numerous boils appeared on her scalp and recurred in crops at various times subsequently.

The patient was residing in Hamilton, Virginia, in Loudon County, at the

time of the onset of her illness. This locality is not more than 10 miles from cases 1, 2, and 3.

She was admitted to Children's Hospital in August, 1922. Physical examination on entry revealed a severely emaciated 4-year old white female who appeared chronically ill. There were numerous furuncles on the scalp. The cervical, axillary, inguinal nodes, liver, and spleen were enlarged. The physical examination was otherwise negative.

During her stay in the hospital she became progressively worse. The temperature remained persistently elevated and the child expired one month after entry.

On postmortem histological examination revealed parasitic organisms which, at the time, were thought to be Leishman-Donovan bodies and a diagnosis of Kala Azar was made. However, upon review of these microscopic sections at a later date by Dr. Oscar Hunter and the pathologists at the Army Medical Museum, Washington, D. C., these organisms were identified as *Histoplasma capsulatum*.

Discussion

Diagnosis: In Darling's[2] original report, he described histoplasmosis as being characterized by splenomegaly, emaciation and prolonged intermittent fever. Subsequent case reports have shown considerable variation in the symptomatology and the physical findings. In their comprehensive summary of reported cases, Parsons and Zarafonetis[6] found an irregular fever to be an almost constant feature, although normal temperature in rare cases may be present during periods of remission. Anemia, hepatomegaly, splenomegaly, lymphadenopathy, and involvement of lungs and adrenals occurred in a majority of cases reviewed by them, while leukopenia, gastrointestinal symptomatology, emaciation, and ulcerations of the mouth were present in approximately $\frac{1}{3}$ to $\frac{1}{2}$ of the patients. Other organs involved with varying frequency were bone marrow, kidney, skin, larynx, pancreas, ear, brain, and heart.

The inconsistency of the presenting symptoms and the fact that histoplasmosis simulates several other diseases makes its clinical diagnosis relatively impossible. In cases of hepatosplenomegaly with depression of the formed elements of the blood, the disease may be confused with aleukemic leukemia. In case 3 of the series reported here, the latter diagnosis was entertained premortem. Similarly the presence of marked lymphadenopathy may simulate Hodgkin's disease, lymphosarcoma, or tuberculous adenitis. In Case G reported by Parsons and Zarafonetis[6], Hodgkin's disease and histoplasmosis were found to coexist. In case 1 reported here, the diagnosis of Hodgkin's disease was seriously considered in view of the marked lymphadenopathy which rapidly disappeared under roentgen therapy. However,

a biopsy of one of the nodes failed to reveal the presence of Dorothy Reed-Sternberg cells. Kala Azar may also present difficulty in the differential diagnosis, but Histoplasma may be differentiated microscopically by its budding manner of growth, thicker wall, and by the lack of a micronucleus.

In view of the chronicity, the intermittent fever, the leukopenia, and anemia which are usually present in histoplasmosis, this disease may simulate brucellosis, malaria, and infectious mononucleosis. It must also be distinguished from syphilis, neoplasm, tuberculosis, and other fungus infections if cutaneous and oro-pharyngeal lesions are present. It must be differentiated from bacillary and amoebic dysentery, tuberculous enteritis and more rarely from idiopathic ulcerative colitis in cases where intestinal ulceration and diarrhea are prominent features of the disease. In case 1 of our series, severe bloody diarrhea persisted for several months prior to death.

The diagnosis of histoplasmosis can be established only by the laboratory demonstration of the fungus. Parsons and Zarafonetis[6] point out in their review of 71 reported cases that in the 9 cases where bone marrow was aspirated, the fungus was found in only 5. In 3 of these 5 cases, the patients were infants. Histoplasma was found in blood smears in only 4 cases. Repeated premortem blood cultures were consistently negative in our cases 1 and 2. This may have been due to the fact that cultures were discarded too soon. Beamer et al.[8] reported that blood cultures may reveal growth as early as the third day following inoculation of the media, but cultures should not be discarded as negative until after incubation for one month. The conclusion seems warranted that examination of blood smears is not a reliable diagnostic procedure since the fungus apparently is present in the circulating blood only intermittently, or only in very small numbers, or only terminally. In both of the new cases reported here, the fungus was demonstrated in smears or cultures of bone marrow made both premortem and postmortem.

Biopsy of lymph nodes, spleen, and ulcers, probably constitutes the most reliable method of making the diagnosis. However, in case 1 of our series, a biopsy of a lymph node failed to show the fungus. Examination of the stools for the presence of Histoplasma was suggested by Henderson and associates[9] in view of the frequent intestinal involvement. There is some suggestive evidence that it may be cultured from the urine with a demonstration by Reid et al.[10] and that it could be recovefed from the urine of guinea pigs which had been infected intravenously with Histoplasma.

Significance of the Histoplasmin Skin Test

A specific skin test would be a valuable aid in the diagnosis of histoplasmosis and the search for a suspected mild form of the disease. Van

Pernis, Benson and Hollinger[11, 12] and Zarafonetis and Lindberg[13] developed a histoplasmin skin test in which sensitized individuals react with erythema and induration at the site of injection of the antigen. Emmons, Olson, and Eldridge[14] reported that 0.1 cc. of a dilution of 1:100 of histoplasmin, prepared by growing *Histoplasma capsulatum* on the synthetic broth medium used in making tuberculin, gave a positive reaction in guinea pigs inoculated experimentally with Histoplasma. They found 34 of 136 persons reacted to both histoplasmin and blastomycin. Plamer[15], investigating the possibility that an infection with Histoplasma may be the cause of non tuberculous pulmonary calcification, found that among student nurses tested with this histoplasmin, the percentage reacting varied from 6.3% in Minneapolis to 65.8% in Kansas City, Mo. He also reported a high degree of correlation between the occurrence of histoplasmin reactions and the presence of pumonary calcification. From these studies, Palmer concluded that Histoplasma or an immunologically related fungus, may account for the presence of pulmonary calcification in tuberculin negative reactors. A corollary of this would be the possibility considered by several investigators that histoplasmosis may be prevalent in central and eastern United States.

Emmons, Olson, and Eldridge[16] have demonstrated that this histoplasmin is not specific in histoplasmosis, but shows cross reactions with blastomycosis, coccidioidomycosis, and haplomycosis, and that, therefore, it is not possible at present to evaluate the clinical or epidemiological significance of the surprisingly high incidence of histoplasmin reactions. Since the publication of this report, the same lot of histoplasmin has been further tested on animals with other experimental mycoses and a cross reaction with *Candida albicans* was demonstrated. This fungus is the cause of thrush in infants and vaginal thrush, and it is often present in the intestinal tract of normal individuals. It is also very commonly present in the sputum as a secondary invader in many kinds of pulmonary diseases. If it is capable of sensitizing man to histoplasmin as it does guinea pigs, this may account for the high incidence of histoplasmin reactions observed. It is apparent that the histoplasmin used in these studies is not a specific diagnostic antigen.

In the two cases which occurred in siblings reported here (cases 1 and 2), both were tested with histoplasmin in dilutions ranging from 1:1000 to undiluted. Neither patient reacted. It seems probable that they were anergic since they were in the terminal stages of the disease when tested. An analogous situation would be the negative tuberculin reaction not uncommonly seen in overwhelming tuberculous infection. Both parents of these siblings reacted to dilutions of 1:1000 of both histoplasmin and blastomycin.

Course

Histoplasmosis may have an acute onset and rapidly fatal termination, or it may appear in a chronic form with irregular exacerbations and long remissions. In the review[6] of 71 cases only 4 patients were still living after 2 to 6 years, and the average course of the disease in 39 cases with a duration of less than one year was 5 months. In children under 12 years of age, the average duration of the disease was approximately 3 months. The durations in the 4 cases reported here were 7 weeks and 7, 12 and 18 months.

Treatment

Many drugs, including the sulfonamides and penicillin, have been tried without benefit in the treatment of histoplasmosis.

Neostam, an antimony compound, has been used in several cases with equivocal results. Mantell et al.[17] reported a case in which definite improvement was noted following its use. In a case treated by Palmer et al.[18] five injections of neostam were administered and the drug was then discontinued because it was poorly tolerated by the patient. Sulfathiazole and other drugs were also given. At autopsy no Histoplasma could be found even though it had been demonstrated in large numbers in a biopsy prior to the institution of therapy. Parsons[6] also observed at least temporary improvement following antimony therapy. The occasional encouraging outcome with neostam would indicate that it warrants further trial.

Source of Infection

The problem of the natural habitat of the fungus poses interesting questions. Although there may be a mild form of this apparently fatal disease, with transmission from person to person there is at present no proof that this is true. So far as we have been able to find, the two cases in brothers reported here represent the only instance of contact between proved cases of histoplasmosis. We do not know whether in this instance there was transmission from one to the other or whether there was merely a common exposure to one source.

The sporadic appearance of the mycosis without recognized association between cases of infection could be interpreted to indicate that it is not primarily a human disease and is not dependent upon an unbroken chain of human infections or human carriers. If this be true, the possible occurrence of some animal host or reservoir should be considered. Histoplasmosis in the dog has been reported by several investigators and the dog is known as a susceptible laboratory animal, but it is not yet known whether this is a

common disease of dogs, transmitted from dog to dog, or whether dog and man are infected rarely and perhaps by accident from a common source. The reports of a disease which may have been histoplasmosis in mice, rats, and a ferret, the susceptibility of mice to experimental histoplasmosis, and the observation by Emmons of what appears to be a reservior of coccidioidomycosis in wild rodents led to a search in the Ashburn area for a rodent reservior of histoplasmosis. A total of 235 rodents were trapped and examined by culture without finding the fungus. Pathological studies on this series of rodents are not yet concluded.

Summary

Four cases of histoplasmosis (two new and two previously reported) occurred in children living in a rural area having a radius of 8 miles. The two new patients were brothers. *Histoplasma capsulatum* was isolated in culture from both. Neither reacted to histoplasmin. The possibility of transmission from one brother to the other is considered. A search for an animal reservoir in this area was not successful. Histoplasmin reactions in guinea pigs with experimental moniliasis are reported.

We wish to express our appreciation to Dr. Joseph S. Wall for his helpful suggestions and advice. We are greatly indebted to Dr. E. Clarence Rice, Pathologist, Children's Hospital, and his staff and to Dr. Carl Larson, United States Public Health Service, for their help in arriving at the diagnosis in Cases 1 and 2. We are also indebted to Dr. Edgar Copeland for his permission to report Case 4 of this series.

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PAROXYSMAL AURICULAR TACHYCARDIA

Case Report No. 50

Dr. Charles Stiegler J. K.—45–8295

This is the case of J. K., a 5½ month old white female infant, who was referred to Children's Hospital October 13, 1945 by a private physician because of a "cold" of 3 days duration with repeated projectile vomiting of feedings and excessive crying on the day of admission. Physical examination revealed a mild infection of the tonsils and pharynx with no other significant findings; the temperature was normal. The infant responded well to symptomatic treatment, and was scheduled to be discharged four days after admission. However, her temperature rose to 101.8° at 4 p.m. on October 16 without any discernible cause other than a mild pharyngitis and it was decided to retain her for further observations. The temperature continued to be periodically elevated over the following 3 weeks.

On October 25 at 1:45 p.m., the infant suddenly developed tachycardia, with a heart rate well over 200 and a markedly accelerated respiratory rate. The patient was pallid and apathetic, but not cyanotic. An EKG taken at 3:30 p.m. showed a regular ventricular rate of 300–310 per minute; the interpretation was supraventricular tachycardia, probably auricular. Fig. 1. The patient was given quinidine sulphate (gr. 1) at 3:30 p.m. without effect, and the dose was repeated at 4:30 p.m. The rate then became slower and preparations were made to repeat the EKG. At 5 p.m. the infant was sleeping comfortably; the pulse rate was 144 per minute. At 5:05 p.m., the patient was awakened preparatory to taking the EKG; there was a bout of projectile vomiting which seemed to duplicate the one prior to admission. The EKG was then taken and showed a sinus tachycardia of 160 per minute. Radiographic examination of the chest at this time showed the left side of the heart to be enlarged.

No further doses of quinidine were given on the 25th and 26th of October and the sinus tachycardia persisted, the rate ranging between 150 and 180. On October 27, the rate suddenly rose to approximately 300 per minute; two one grain doses of quinidine sulphate at an hour's interval were given, with a slowing of the rate to a sinus tachycardia ranging between 150-180 per minute. As the rate did not approach normal over the next 3 days and showed elevations to 180-200 per minute, the infant was placed on quinidine sulphate gr. ½ every 6 hours. When no further response was obtained, the dosage was doubled November 1 without any persistent slowing of the rate. Calcium gluconate, 10 cc. of a 10% solution, was

given intravenously on November 2 and 5, with only a transient slowing of the rate.

On November 5, digitalization was begun with an initial dose of 2 cat units followed by grains $\frac{3}{4}$ daily; the quinidine was discontinued for 24

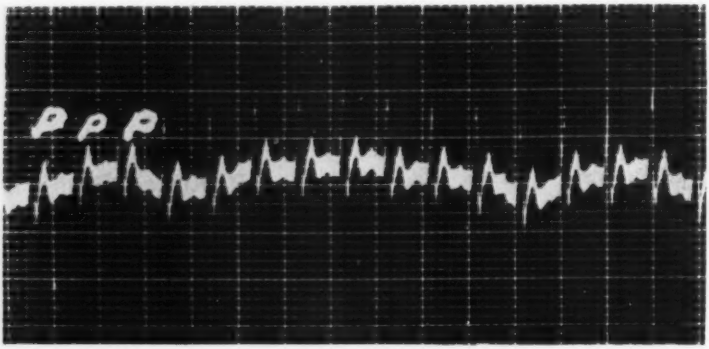

FIG. 1. J. K. ELECTROCARDIOGRAM TAKEN OCTOBER 25, 1945 AT 3:30 P.M., ONE HOUR AND 45 MINUTES AFTER THE ONSET OF THE TACHYCARDIA; REGULAR VENTRICULAR RATE OF 300-310 PER MINUTE
Interpretation: supraventricular tachycardia, probably auricular

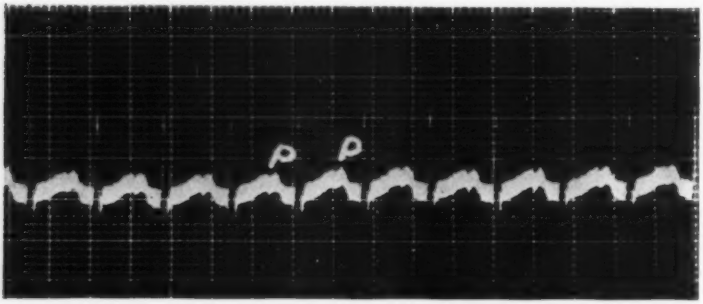

FIG. 2. J. K. ELECTROCARDIOGRAM TAKEN OCTOBER 25, 1945 AT 5:30 P.M., AFTER THE ADMINISTRATION OF QUINIDINE GRAINS 1 AT 3:30 P.M. AND 4:30 P.M.
Regular ventricular rate of 160 per minute; interpretation: sinus tachycardia

hours, but started again because of a rapidly rising pulse rate. On November 11, the rate dropped to 120 per minute and the daily dose of digitalis was reduced to grains $\frac{1}{2}$. On November 15, the digitalis was discontinued as the rate was persistently normal. Attempts to discontinue or reduce the maintenance dose of quinidine were unsuccessful, with prompt elevation of the pulse rate after each attempt. The infant was discharged

from the hospital December 3, 1945 on a maintenance dosage of quinidine sulphate (grains 1) every 6 hours; the discharge diagnosis was paroxysmal auricular tachycardia.

On December 5, 1945 the infant was readmitted because of vomiting, fever, cough, and a recurrence of the tachycardia; the temperature was 101.2°7and the heart rate approximately 200 per minute. The physical examination revealed a mild tonsillo-pharyngitis. The upper respiratory infection responded to penicillin therapy, which was discontinued December 10. Because of a persistently fast heart rate, quinidine grains 1 was given at 2 or 4 hour intervals as indicated, but the tachycardia of 150-220 per minute persisted. The temperature became elevated to 103.2° on December 15, and penicillin therapy was reinstituted, with a gradual return of the temperature to normal on December 19 and 20. On December 21, the patient's temperature rose to 105° without any apparent cause. Sulfadiazine was given in addition to the penicillin and the temperature became normal on December 23. From December 23 until discharged, periodic elevations to 100° were encountered; the penicillin and sulfadiazine were discontinued December 28.

The patient was discharged to the Children's Country Home on a maintenance dose of quinidine sulphate grains 1 every 4 hours; the heart rate was still 150–200 at the time of discharge on January 8, 1946. At the Country Home, the patient has been doing well on the maintenance dose of quinidine. An EKG was taken April 29, 1946 which showed a regular ventricular of 138 per minute; interpretation: sinus tachycardia.

Discussion

Paroxysmal tachycardia was considered a rare entity in infancy until Hubbard first pointed out, in his review of 9 cases, the ease with which the diagnosis can be overlooked.

In older children, the attacks are usually characterized by an abrupt onset, a duration varying from moments to several days, and a sudden termination. Palpitation and precordial distress is the most common present symptom, although symptoms of congestive failure may develop rapidly if the paroxysm persists. Clinically these cases may be suspected from the presence of a rapid, regular heart rate of about 200 beats per minute. The rate is usually faster than that found either in simple sinus tachycardia or auricular flutter, and the duration of the paroxysm is usually shorter than an auricular fibrillation. The paroxysm may subside spontaneously but it is less apt to respond to simple procedures such as carotid sinus pressure, than is a similar paroxysm in an adult. If medication is necessary, digitalis or quinidine may be used to return the heart rate to normal. In some cases the tachycardia may recur after the medication

is stopped; in these cases it may be necessary to place the child on a maintenance dose of the drug until the paroxysms subside. Mecholyl has been used with success in terminating paroxysmal tachycardia, but the occurrence of side reactions seems especially prone to occur in children. For this reason, it may be best to use mecholyl only in those cases which fail to respond to other forms of therapy.

The occurrence of paroxysmal tachycardia in infants, as illustrated by the case reported, presents certain additional factors for consideration. Because of the occurrence of faster heart rates in infants in response to such factors as excitement or infections, the possibility of a paroxysmal supraventricular tachycardia is apt to be overlooked. In Hubbard's series of cases, the ventricular rate varied from 220–305 beats per minute as determined electrocardiographically. In 7 of the 9 cases, there was no associated pathology in other systems of the body; the 7 infants were under one month of age.

The characteristic onset in the infant age group is an episode of vomiting associated with restlessness, prostration, and a grayish color of the skin. The ventricular rate is regular and so fast as to be difficult to count; the pulse is rapid, and may be too feeble to palpate. Signs of congestive failure usually appear rather quickly if the paroxysm persists, as it is apt to do in infants. Because of the tendency for paroxysms to be of prolonged duration in infants, it is important not to delay treatment so as to combat and/or prevent the appearance of congestive heart failure. Digitalis or quinidine may be used; Hubbard recommends giving digifoline intramuscularly in doses of 0.05–0.1 gm., and repeating the dose as indicated by the response obtained. As in older children, recurrences may occur, necessitating the administration of maintenance doses of the drug used until the paroxysms subside. With the subsidence of the paroxysm, a dramatic improvement may be noted clinically, with rapid disappearance of the signs of congestive failure.

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CONGENITAL BILIARY ATRESIA

Case Report No. 51

Dr. Charles Stiegler M. A.—45-2501

This is the case of M. A., a white female infant, who was admitted to Children's Hospital on March 27, 1945 at the age of 4½ weeks because of jaundice. She was born February 20, 1945, a breech extraction with forceps to the aftercoming head. An x-ray of the skull shortly after birth revealed a basilar fracture, but there was no increase in intracrainial pressure. An x-ray of the skull on March 15th showed the fracture to be healing well. The infant's birth weight was 5 lbs. 14¼ oz.

Icterus was first noted on the third day of life; the stools were clay colored. The jaundice was becoming less marked at the time of admission to this hospital, but the stools were still persistently clay colored. She had been on an evaporated milk formula since birth, taking and retaining feedings well. Her weight on admission was 7 lbs. 6 oz. and she was afebrile. The significant findings on admission were the presence of mild generalized jaundice, the palpation of the liver 3 fingers below the costal margin, and a moderately enlarged spleen. A Kahn and Mazzini were negative, and examination of the stool was negative for bile. The van den Bergh reaction was immediate and direct; quantitatively, there was 5.1 mgm. of bilirubin per 100 cc. of blood. The prothrombin time was 96% of normal, and a hemogram showed 11 gm. hemoglobin, 3.31 million erythrocytes, with a normal leucocyte count and differential. The urine was strongly positive for bile. The working diagnosis was a congenital anomaly of the biliary tracts producing an obstructive jaundice. Continued observation and repeated laboratory studies, while the patient was being prepared for surgical exploration, supported the admission diagnosis. An exploration of the biliary tract was made on April 26, 1945. At that time a small catheter was inserted into the biliary tree in an effort to establish an external biliary fistula to be anastomosed at later operation to the gastro-intestinal tract.

Because of continued drainage of bile and a failure of the bile to drain through the catheter, it was believed that a sinus tract would not form; accordingly, an anastomosis of the gall bladder to the stomach was made on June 2. Following this second operation, the patient eviscerated twice through the wound, on June 7 and June 12; in both instances, it was difficult to maintain sterile technique in replacing the abdominal contents before the infant could be taken to the operating room. After the second evisceration the cholecystogastric anastomosis was explored externally and showed

no unusual changes. An opening was made into the stomach and the anastomosis site was explored and found strictured. Several silk sutures were removed from within the stomach at the site of anastomosis and the opening was dilated. A small amount of bile was found above the anastomosis. The gastric opening was then closed and the abdominal wall was approximated with interrupted through and through sutures.

The patient ran a stormy course, with abdominal distension, fever ranging from 100–104°, continued jaundice and clay colored stools. She was given repeated blood transfusions and penicillin 10,000 units intramuscularly every 3 hours was administered from June 11 to June 19. Because of an exacerbation of fever, the penicillin was started again on June 21 and continued during the next two weeks. The stools were positive for bile on June 16 for the first time, two weeks after the anastomosis was made; the jaundice persisted, but was less marked. Her condition at this time was poor.

She began to improve slowly the first week in July with decreasing jaundice, increasingly yellow stools, and an afebrile course; she was taking and retaining feedings, and gaining weight satisfactorily. The infant was discharged from this hospital July 18, 1945, on her 145th hospital day; there was a moderately severe incisional hernia at the time of discharge.

The patient was readmitted to the hospital on February 18, 1946; the interim course since her previous admission was uneventful. A repair of the incisional hernia was done March 7. At that time an attempt was made to visualize the anastomosis but abundant scar tissue surrounded the site and it was believed advisable not to disturb the tissue in that area. Her postoperative course has been uneventful, and the repair has healed well.

Case No. 2

The second case is that of a white male infant who was admitted to the Children's Hospital on February 12, 1946 at the age of 6 weeks because of jaundice.

The patient was born at term on January 1, 1946; the delivery was normal. He has been bottle fed since birth. When the mother was ready to leave the hospital after an uneventful postpartem course, she was advised to leave the baby there a few more days with no reason being given. The child was discharged from the hospital at 3 weeks of age, at which time the mother states "his skin and eyes were yellow." At home, the infant was put on a formula of skimmed milk and Karo, which was taken and retained well. The stools throughout this period were pasty and pure white in color, without any noticeable odor; the urine was a deep golden yellow. These findings persisted until admission to this hospital.

The mother has two other children, both normal deliveries with uneventful neonatal courses; there were no other pregnancies. There was no history of Rh studies being done during confinement and no history of the mother receiving any transfusions prior to gestation.

Physical examination on admission revealed a well-nourished, well-developed 6 weeks old white male infant, jaundiced but in no apparent distress. The weight on admission was 10 pounds 5 ounces, and the temperature was 99° by rectum. The only other significant physical findings were a pronounced icteric tint of the sclerae; the liver was palpable 3 fingers below the costal margin with a firm, smooth, non-tender edge; the spleen was palpable 1 finger below the costal margin. A tentative diagnosis of a congenital anomaly of the biliary tracts was made, with erythroblastosis foetalis accompanied by obstruction of the biliary tracts to be ruled out.

A hemogram on admission showed 9.5 grams of hemoglobin, 3.11 million red blood cells, 9,400 leucocytes with a normal differential. The stool examination was negative for bile on February 14. The Rh factor was positive for mother and patient; Kahn and Wasserman were negative. The icteric index showed 34 units, and the van den Bergh showed an immediate direct reaction with 4.1 mgm. of bilirubin per 100 cc. on quantitative examination.

The patient was placed on a high carbohydrate, low fat formula. Under observation, the jaundice increased in intensity and the stools continued to be clay-white in color, with a negative reaction for bile on laboratory examination. Because of the clinical picture and the laboratory findings, a biliary tract exploration was planned; preoperative care included two 100 cc. transfusions of citrated blood, Hykinone ampoules 1 daily for 4 days; and amigen clyses twice daily for 3 days. On February 19 the bleeding time was less than 1 minute, the coagulation time 4 minutes 45 seconds.

On February 21, an exploration of the bile ducts was done through a right rectus incision. The gall bladder appeared collapsed and empty. The common duct was identified and appeared normal in the lower portion of its course, but looked small above the juncture with the cystic duct. A definite bifurcation of the hepatic ducts could not be demonstrated. The gall bladder and the common duct were aspirated with a fine needle and syringe, but no bile was obtained; both the gall bladder and the common duct were injected with saline, and the fluid seemed to enter without much pressure. There was slight distension of the common duct in its lower portion, but not in the upper portion. The abdomen was closed without drainage.

The postoperative course has been slowly downhill with increasingly severe jaundice, continuation of the clay-white stools, and a slow, steady weight loss. A stool examination for bile was negative on March 1. The

incision healed slowly, the sutures being removed March 2. The patient was discharged from the hospital on March 6, condition unchanged. The diagnosis on discharge was congenital anomaly of the biliary ducts.

Discussion

Dr. Ogle Warfield*

Surgery offers the only hopeful means of therapy in infants with congenital atresia of the biliary tracts. In the great majority of such infants, surgery is not successful. However, there is a small percentage of cases (Ladd and Gross, 20%) which are operable. All infants, therefore, definitely diagnosed as having congenital atresia of the biliary ducts should be explored. Adequate exposure, a dry field and delicate dissection are important.

An atretic biliary duct appears as a fine, white cord or thread. Aspiration of bile from the hepatic duct, common duct or gall bladder will locate the areas of atresia between the point of aspiration and the duodenum. Injection of saline into these same structures will sometimes open a duct which has been blocked with inspissated bile or mucous. If bile can be obtained from the ducts or gall bladder, then an anastomosis should be attempted between that portion of the extra hepatic biliary tract and the duodenum. Such anastomoses are best done over a short, fine piece of rubber tubing to avoid subsequent stricture. The tubing is later expelled into the intestinal tract.

Baby W., (case 2) was found to have complete atresia of the entire extent of the common bile duct. No clearly defined hepatic ducts could be demonstrated and attempted aspiration and injection of saline were unsuccessful. Case 1, on the other hand, had a patent hepatic and cystic duct and a successful anastomosis was possible.

* Chief of the Surgical Staff, Children's Hospital.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by Dr. E. Clarence Rice

Assisted by Dr. Clifford J. Tichenor

Case Report No. 52

Dr. Clifford Tichenor

S. R., a seven year old white male, entered the hospital complaining of pain in the lower left thigh. One month before admission he first noticed a "nagging" pain in this area which was attributed to a fall from the "monkey bars" at school at about this time. At first the pain appeared in the left popliteal fossa, but in three days had shifted to the lower left anterior thigh and had increased in intensity. One week prior to admission he walked with a limp and with increasing difficulty.

The past history was negative except for uncomplicated measles and otitis media at the age of five. The birth history was non-contributory, the infant being full term, born of a healthy multipara in her late thirties; labor was of four hours duration and uncomplicated. The birth weight was seven pounds, the weight increment was progressive, and the infant walked and talked at one year. The family history was negative for tuberculosis, syphilis, epilepsy, insanity, dystrophies, and allergic manifestations.

Physical examination revealed a somewhat pale child of about the stated age, appearing to have lost weight recently, but in no acute distress. Examination of the head, neck, heart, lungs and abdomen was negative. Measurement of the left thigh at the junction of the middle and lower third was 28.5 centimeters. Measurement of the right thigh in this area was 25 centimeters. Attached to the lower left femur anteriorly was a tender, hard mass, having a spindle shape and the size of a large lemon. There was no limitation of the left hip or knee joints, but the patient refused to bear full weight on this left leg because of pain. No lymphadenophaty was evident.

The temperature was 99°F., the pulse was 90 and the respiration was 20. The blood pressure was 110 systolic, 76 diastolic.

The hemoglobin was 12.5 gm., erythrocytes 4,190,000. The white blood count was 5,900 with 71% neutrophils. The red cells and platelets appeared normal in a stained smear. The Kahn and tuberculin tests were negative. The urine was normal.

X-ray examination of the left femur showed a destructive lesion in the lower third involving both the cortex and the medulla (fig. 1). There were also perpendicular periosteal striations extending into the soft tissue,

as well as laminated periostitis extending into the upper and middle third of the shaft of the femur. A provisional x-ray diagnosis of Ewing's endothelimoa was made and deep roentgen therapy was considered advis-

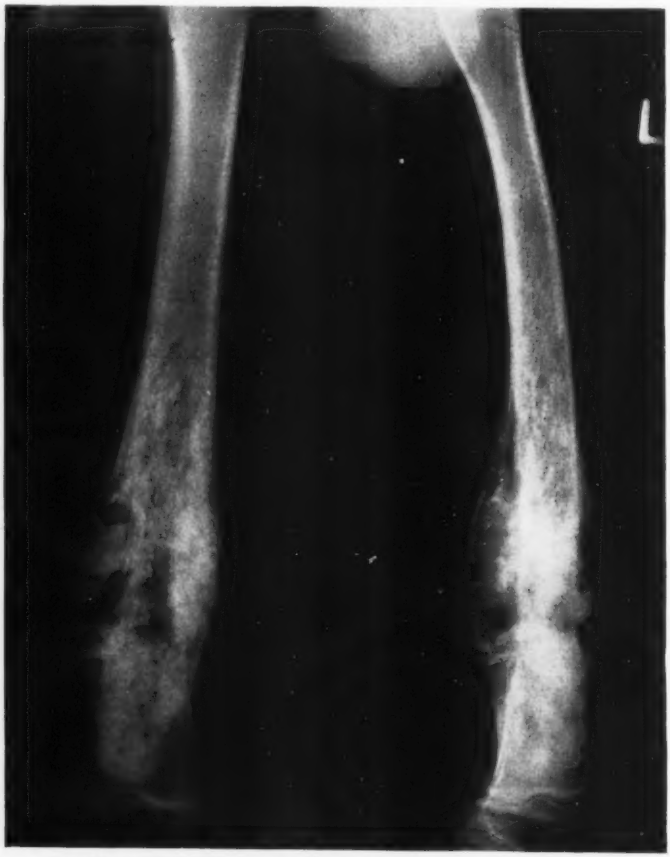

FIG. 1. S. R. NOTE THE TRANSVERSE SPICULES OF NEW BONE WITH RUPTURE OF THE PERIOSTEUM

able. The chest showed two circular shadows rather far out into the left base and about 6 mm. in diameter suggestive of pulmonary metastasis.

No other bony lesions were found and the patient was discharged on the fifth day condition unchanged, and admitted for deep x-ray treatment.

Two months later the child was readmitted to Children's Hospital with a

temperature of 102.4°, pulse 160, respirations 55 and appearing acutely ill with marked respiratory difficulty. He appeared generally asthenic, undernourished and had lost 12 pounds since his last admission.

There had been no improvement under treatment during the interim, clinically or radiographically, and the child had been consistently nauseated with occasional vomiting. Marked anorexia had developed along with weakness and the weight loss was very apparent.

Physical examination at the time of this second admission revealed the heart rate to be very rapid, but no murmurs were heard. The sounds were regular but distant. The right chest was clear, but there was flatness over the entire left chest with markedly diminished to absent breath sounds anteriorly and posteriorly. The left side had a visible excursional lag and the interspaces revealed some bulging. The heart was apparently displaced to the right. The abdomen was scaphoid with generalized tenderness especially noted in the left upper quadrant. Attached to the lower left femur was the tender, hard mass somewhat obscured by swelling, redness and induration of the immediate surrounding soft tissues. There were no disturbances of the sensory or motor nerves.

The hemoglobin was 4.5 gm., erythrocytes 1,690,000. The white blood count was 12,100 with 88% neutrophils. The urine showed a positive acetone but was otherwise negative. The tuberculin test was again negative in 1:100 dilution.

X-ray of the chest showed a massive pleural effusion on the left side. The right lung field was studded with metastatic areas. Radiographically the tumor previously reported in the left femur had not regressed following deep therapy, suggesting that the diagnosis was one of osteogenic sarcoma rather than Ewing's tumor.

Paracentesis of the left chest was performed on the second day and 400 cc. of thin red cloudy fluid was removed. This procedure relieved the severe dyspenea somewhat.

On the sixth day a whole blood transfusion of 175 cc. was given without apparent improvement. The progress was rapidly and progressively downhill and the child expired on the 24th day of his second admission. Necropsy was performed.

Differential Diagnosis

Dr. John Nestor: The first essential point to be considered in this diagnosis is whether the lesion is inflammatory or neoplastic. I shall discuss inflammatory lesions first.

Osteomyelitis is one of the commonest of the inflammatory lesions. In favor of this diagnosis are the age of the patient, the pain, and the progressive character of the process. Against it are the x-ray evidence of destruc-

tion of the periosteum and the lack of sequestration and new-bone formation usually seem in an osteomyelitis of relatively long duration. Osteomyelitis will raise the periosteum, but seldom penetrate it. The site of the lesion, however, is not unusual for such a process. The white cell count may be elevated but not necessarily so, especially in the more chronic phase of the disease.

Tuberculosis usually involves the epiphysis of bone and is seldom seen without other manifestations of the disease. According to Dr. Ira Nathanson of the Massachusetts General Hospital, tuberculosis usually arises in the neighborhood of a joint and involves the capsule and cartilage.

Syphilis can be eliminated on the basis of the character of the lesion, the age of the patient, the negative serology and the absence of any other evidence.

Rarely such condition as eosinophilic granuloma is seen in young children and may occur at any bony site, but generally in flat bones. These do give rise to symptoms of pain and evidence of tumor. It is seldom debilitating however and does not produce the course of events as seen in this patient. Osteoid osteomas also occur rarely but the lesion is small, limited and causes few symptoms.

I would say that the history, symptoms, physical findings and laboratory work strongly suggest a neoplastic process. Osteochondroma is ruled out immediately by the x-ray.

The course of this illness makes me lean toward the malignant lesions and the possibilities here I believe constitute the essence of our problem.

A malignant lymphoma involving bone, especially the reticulum-cell sarcoma type could primarily arise in a single bone I suppose and remain confined to a single location for a considerable time. It is usually slow growing, however, and seldom has constitutional symptoms even when large. The x-ray is against such a diagnosis.

Osteogenic sarcoma must be strongly considered. This occurs more in males according to Ewing and generally arises in the metaphyses of long bones and having the greatest incidence in the second decade. The region of the knee is a favorite site. The history of trauma is always a doubtful point to use in evaluating malignant tumors. An alkaline phosphatase level would be helpful here, especially if it were elevated. Pain is frequently an early symptom and disability is usually absent until very late. Osteogenic sarcoma spreads by blood stream, especially to the lungs and metastasis to other bones is rare. Even through the x-ray films show periosteal reaction, this in itself is insufficient to make a diagnosis.

Myeloma usually occurs in persons over forty and is generally present in multiple sites when the patient is first seen. Metastatic lesions from primary tumors elsewhere are very unusual in this age group and seldom give rise to soft tissue tumors.

Another tumor to be strongly considered is Ewing's sarcoma. This is a tumor of growing bone and arises from the bone marrow. There is often a history of trauma preceding this growth and pain and swelling are a part of the clinical syndrome. The long bones are usually affected and the disease causes bone destruction as it develops and by x-ray the bone has a moth eaten appearance. The periosteum becomes reactive and lays down new bone, often in layers, giving the so-called characteristic onion-skin appearance. When radiating spicules are present, it can readily be confused with osteogenic sarcoma. It is more common in females according to Ewing and occurs most frequently in the neighborhood of twenty. This disease may also penetrate the periosteum and invade the surrounding soft tissue. It is palpated as a tender, firm, irregular mass and the overlying skin may be warm, red and edematous. Bouts of febrile reactions are often seen with Ewing's tumor, as well as constitutional changes such as weakness and loss of weight. Motor and sensory nerve involvement are frequent disturbances arising from this growth. This tumor has a propensity to set up metastasis in other bones, especially the skull. No mention was made of a skull x-ray in the history. The lungs may also be involved. A point of special importance is the remarkable reaction to radiation. Here I find a stumbling block, because the history relates that no radiologicol improvement was ever noted from deep therapy.

In summary this patient does present a picture of malignant tumor exactly fitting the clinical syndrome. In view of the above facts, however, the most probable diagnosis is Ewing's sarcoma with pulmonary metastasis. My second choice would be osteogenic sarcoma with pulmonary metastasis

Pathological Discussion

The autopsy dissection of the left femur revealed an area of new growth over the medial lower surface measuring approximately 8.0 by 3.5 cm. It sectioned with decreased resistance, having a spongy hemorrhagic, partially calcified appearance.

The pleural cavities had dense adhesions throughout, there being an hemorrhagic growth about 14.5 by 4 cm. attached to the left sternal border about the level of the sixth costal cartilage.

The right lung weighed 450 gms., the left 570 gm. There were dense adhesions throughout, more marked over the bases and lateral borders, resulting in considerable traumatization to the pulmonary tissue. The normal appearance was obliterated, the tissue being replaced by innumerable nodules varying in size from 0.2 to 4 cm. in diameter and in color from a light gray to a dark purplish blue. Some consisted of an osteoid-like tissue, others being filled with blood. The larger growths proved to be of the vascular type.

The anatomical diagnosis was osteo-sarcoma of the left femur, with pulmonary metastasis.

Cytology Discussion

Dr. J. Lindsey: Sections from bone show structures varying from that of rather typical osteofibrosis, with well developed and well preserved bony trabeculae, to areas in which the marrow is replaced by evidently neoplastic tissue of mesoblastic origin. The nuclei in these areas vary greatly in size and morphology, many large more or less lobulated forms, some apparently multinucleated. No systematic arrangement of the cells is noted. There are areas of necrosis and occasional mitotic figures are seen. In some areas there is a suggestion of lamination such as might be expected in periosteal tumors. However, the process is considered to be of osteogenic type with evidence of both bone destruction and production.

In the lung there are plaques of cellular structure essentially the same as those described in the bone and certainly representing metastasis from the latter.

Pathological Diagnosis

Dr. E. Clarence Rice: This tumor is probably an osteo-sarcoma.